WEST Search History

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DATE: Monday, May 01, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L19	L18 and l17	14
☐	L18	l16 and selenium	32
☐	L17	L16 and retinoid	21
☐	L16	L15 and treatment	84
☐	L15	L14 and glutathione adj peroxidase	86
☐	L14	HCV	7569
☐	L13	Munchen S.in.	1
	DB=EPAB; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L12	DE-10255861-A1.did.	1
☐	L11	DE-10255861-A1.did.	1
	DB=PGPB,USPT,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L10	L9 and glutathione adj peroxidase	3
☐	L9	Cotten m.in.	32
☐	L8	L7 and glutathione adj peroxidase	5
☐	L7	Herget T.in.	10
☐	L6	L5 and glutathione adj peroxidase	1
☐	L5	L1 and HCV	61
☐	L4	L1 and l2	5
☐	L3	424/228.1.ICLS.	133
☐	L2	424/228.1.ICLS.	133
☐	L1	424/93.2.ICLS.	1637

END OF SEARCH HISTORY

WEST Search History

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DATE: Monday, May 01, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L19	L18 and l17	14
☐	L18	l16 and selenium	32
☐	L17	L16 and retinoid	21
☐	L16	L15 and treatment	84
☐	L15	L14 and glutathione adj peroxidase	86
☐	L14	HCV	7569
☐	L13	Munchen S.in.	1
	DB=EPAB; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L12	DE-10255861-A1.did.	1
☐	L11	DE-10255861-A1.did.	1
	DB=PGPB,USPT,EPAB,JPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ		
☐	L10	L9 and glutathione adj peroxidase	3
☐	L9	Cotten m.in.	32
☐	L8	L7 and glutathione adj peroxidase	5
☐	L7	Herget T.in.	10
☐	L6	L5 and glutathione adj peroxidase	1
☐	L5	L1 and HCV	61
☐	L4	L1 and l2	5
☐	L3	424/228.1.ICLS.	133
☐	L2	424/228.1.ICLS.	133
☐	L1	424/93.2.ICLS.	1637

END OF SEARCH HISTORY

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NEWS	17	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	18	MAR 08	X.25 communication option no longer available after June 2006
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NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
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V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
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=> "glutathione peroxidase"
L1 30666 "GLUTATHIONE PEROXIDASE"

=> HCV
L2 33362 HCV

=> L1 and L2
L3 28 L1 AND L2

=> gastroiintestinal
L4 0 GASTROIINTESTINAL

=> gastrointestinal
L5 184440 GASTROINTESTINAL

=> L5 and L3
L6 9 L5 AND L3

=> D L6 IBIB ABS 1-9

L6 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1331259 CAPLUS
DOCUMENT NUMBER: 144:64327
TITLE: Use of selenium or a selenium salt and a retinoid acid or a retinoid in the treatment of viral hepatitis C
INVENTOR(S): Herget, Thomas; Klebl, Bert
PATENT ASSIGNEE(S): GPC Biotech A.-G., Germany
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005120479	A1	20051222	WO 2005-EP6226	20050609

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-578161P P 20040609

AB The present invention relates to combination therapies comprising at least one retinoid or retinoid agonist together with selenium or a selenium salt particularly useful in conjunction with conventional antiviral therapeutics which are synergistically effective against Hepatitis C virus (**HCV**) infections. In particular, the present invention relates to the synergism between compds. capable of activating or upregulating the **gastrointestinal** form of **glutathione peroxidase** for prophylaxis and/or treatment of **HCV** infections, administered in combination therapies with interferons. The combinations disclosed have proven surprisingly effective even in patients unresponsive to interferon/ribavirin therapies.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:204131 CAPLUS

DOCUMENT NUMBER: 142:277684

TITLE: Expression of **Gastrointestinal Glutathione Peroxidase** Is Inversely Correlated to the Presence of Hepatitis C Virus Subgenomic RNA in Human Liver Cells

AUTHOR(S): Morbitzer, Monika; Herget, Thomas

CORPORATE SOURCE: AXXIMA Pharmaceuticals AG, Munich, 81377, Germany

SOURCE: Journal of Biological Chemistry (2005), 280(10), 8831-8841
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB There is great medical need to develop novel therapies for treatment of human hepatitis C virus (**HCV**). By gene expression anal. of three **HCV**-subgenomic RNA replicon cell lines, we identified cellular proteins whose expression is affected by the presence of **HCV** and therefore may serve as drug targets. Data from cDNA array filter hybridization, as well as from Northern and Western blotting, revealed that the **gastrointestinal-glutathione peroxidase** (GI-GPx) was drastically down-regulated (up to 20-fold) in all replicon cell lines tested. Concomitantly, total cellular **glutathione peroxidase** activity was drastically reduced, which rendered these human liver cells more susceptible toward oxidative stress. Interferon α caused down-regulation of the **HCV** -replicon followed by recovery of GI-GPx expression to nearly normal levels. Furthermore, expression of GI-GPx in replicon cells by gene transduction caused down-regulation of **HCV** RNA in a dose-dependent manner. Moreover, activating the endogenous gene coding for GI-GPx by all-trans-retinoic acid (RA) was sufficient to cause down-regulation of the **HCV** replicon. A small interfering RNA duplex abrogated GI-GPx up-regulation by RA and concomitantly suppression of **HCV**. The RA effect was dependent on the presence of sodium selenite, was reversible, and was independent of RNA-activated protein kinase. Taken together, these results show that **HCV** inhibits the expression of GI-GPx in replicon cells to promote its intracellular

propagation. Modulation of GI-GPx activity may open new avenues of treatment for **HCV** patients.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:633154 CAPLUS
DOCUMENT NUMBER: 141:167729
TITLE: **Gastrointestinal glutathione peroxidase** as therapeutic target for treatment of **HCV** infection, methods of treating **HCV** infection, and compounds useful therefor
INVENTOR(S): Herget, Thomas; Cotten, Matthew; Obert, Sabine; Klebl, Bert
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 24 pp., Cont.-in-part of U.S. Pat. Appl. 2003 180,719.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004152073	A1	20040805	US 2003-723719	20031126
WO 2002084294	A2	20021024	WO 2002-EP4167	20020415
WO 2002084294	A3	20031030		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10255861	A1	20040617	DE 2002-10255861	20021129
US 2003180719	A1	20030925	US 2003-342054	20030114

PRIORITY APPLN. INFO.:		
US 2001-283345P	P	20010413
WO 2002-EP4167	A2	20020415
DE 2002-10255861	A	20021129
US 2002-430367P	P	20021203
US 2003-342054	A2	20030114

AB The present invention relates to the human cellular protein **glutathione peroxidase-gastrointestinal** as a target for medical intervention against Hepatitis C virus (**HCV**) infections. Furthermore, the present invention relates to a method for the detection of compds. useful for prophylaxis and/or treatment of hepatitis C virus infections and a method for detecting hepatitis C virus infections in an individual or in cells. Also compns., compds., nucleic acid mols. (such as aptamers), mono- or polyclonal antibodies are disclosed which are effective for the treatment of **HCV** infections, and methods for prophylaxis and/or treatment of hepatitis C virus infections or for the regulation of hepatitis C virus production are disclosed. The inventors designed a randomized, single-blinded clin. study to test the safety, tolerability, and efficacy of all-trans retinoic acid alone or in combination with pegylated α interferon in patients with chronic hepatitis C. The therapy regimens include: Vesanoid (orally administered all-trans retinoic acid compound, Hoffman-La Roche); Pegasys (slow-release pegylated interferon α2a, Hoffman-La Roche); and selen 30 ALLACT (supplement containing selenium and ALLACT composed of garlic powder and Lactobacillus bulgaricus).

L6 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:490732 CAPLUS
DOCUMENT NUMBER: 141:42933
TITLE: Formulations useful against hepatitis C virus

infections
INVENTOR(S): Herget, Thomas; Klebl, Bert
PATENT ASSIGNEE(S): Axxima Pharmaceuticals A.-G., Germany
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004050101	A2	20040617	WO 2003-EP13514	20031201
WO 2004050101	A3	20040910		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10255861	A1	20040617	DE 2002-10255861	20021129
DE 10305138	A1	20040826	DE 2003-10305138	20030207
CA 2509955	AA	20040617	CA 2003-2509955	20031201
AU 2003294757	A1	20040623	AU 2003-294757	20031201
EP 1567172	A2	20050831	EP 2003-785699	20031201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006514094	T2	20060427	JP 2004-570683	20031201

PRIORITY APPLN. INFO.:

DE 2002-10255861	A	20021129
US 2002-430367P	P	20021203
DE 2003-10305138	A	20030207
US 2003-446246P	P	20030211
WO 2003-EP13514	W	20031201

AB The present invention relates generally to chemical compds. and substances which are effective against Hepatitis C virus (**HCV**) infections. Moreover, the present invention relates to compns. comprising said compds. and/or substances, to methods for preventing **HCV** infections as well use of the compds. and/or substances for the preparation of compns. useful for the prophylaxis and/or treatment of **HCV** infections. Useful compds. and substances according to the invention are selenium, selenium salts, Vitamin D3 and retinoids, like all trans retinoic acid and salts thereof, C1-C10 alkyl amide of all trans retinoic acid and salts thereof, C1-C10 alkyl esters of all trans retinoic acid and salts thereof, 9-cis retinoic acid and salts thereof, C1-C10 alkyl amide of 9-cis retinoic acid and salts thereof, C1-C10 alkyl esters of 9-cis retinoic acid and salts thereof, (E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetra methyl-2-naphthalenyl-1)-propenyl] benzoic acid (TTNPB), (4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] carboxamido) benzoic acid (AM-580), N-(4-hydroxyphenyl) retinamide (4-HPR), and 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (AHPN).

L6 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:757185 CAPLUS
DOCUMENT NUMBER: 139:271014
TITLE: Human cellular protein **gastrointestinal glutathione peroxidase** as target for medical intervention against hepatitis C virus infections
INVENTOR(S): Herget, Thomas; Cotten, Matthew; Obert, Sabine
PATENT ASSIGNEE(S): Germany
SOURCE: U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of Appl. No. PCT/EP02/04167.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003180719	A1	20030925	US 2003-342054	20030114
WO 2002084294	A2	20021024	WO 2002-EP4167	20020415
WO 2002084294	A3	20031030		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10255861	A1	20040617	DE 2002-10255861	20021129
US 2004152073	A1	20040805	US 2003-723719	20031126

PRIORITY APPLN. INFO.:	US 2001-283345P	P	20010413
	WO 2002-EP4167	A2	20020415
	DE 2002-10255861	A	20021129
	US 2002-430367P	P	20021203
	US 2003-342054	A2	20030114

AB The present invention relates to the human cellular protein **glutathione peroxidase-gastrointestinal** as a target for medical intervention against Hepatitis C virus (**HCV**) infections. Furthermore, the present invention relates to a method for the detection of compds. useful for prophylaxis and/or treatment of Hepatitis C virus infections and a method for detecting Hepatitis C virus infections in an individual or in cells. Also compns., compds., nucleic acid mols. (such as aptamers), mono- or polyclonal antibodies are disclosed which are effective for the treatment of **HCV** infections, and methods for prophylaxis and/or treatment of Hepatitis C virus infections or for the regulation of Hepatitis C virus production are disclosed.

L6 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2002:814448 CAPLUS
DOCUMENT NUMBER:	137:291285
TITLE:	Human cellular protein **gastrointestinal glutathione peroxidase** as target for medical intervention against hepatitis c virus infections
INVENTOR(S):	Herget, Thomas; Cotten, Matthew; Obert, Sabine
PATENT ASSIGNEE(S):	Axxima Pharmaceuticals Ag, Germany
SOURCE:	PCT Int. Appl., 37 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002084294	A2	20021024	WO 2002-EP4167	20020415
WO 2002084294	A3	20031030		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2443525	AA	20021024	CA 2002-2443525	20020415

EP 1377833	A2	20040107	EP 2002-730159		20020415
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004533822	T2	20041111	JP 2002-581997		20020415
US 2003180719	A1	20030925	US 2003-342054		20030114
US 2004152073	A1	20040805	US 2003-723719		20031126
PRIORITY APPLN. INFO.:			US 2001-283345P	P	20010413
			WO 2002-EP4167	W	20020415
			DE 2002-10255861	A	20021129
			US 2002-430367P	P	20021203
			US 2003-342054	A2	20030114

AB The present invention relates to the human cellular protein **glutathione peroxidase-gastrointestinal** as potential targets for medical intervention against Hepatitis C virus (**HCV**) infections. Furthermore, the present invention relates to a method for the detection of compds. useful for prophylaxis and/or treatment of Hepatitis C virus infections and a method for detecting Hepatitic C virus infections in an individual or in cells. Also mono- or polyclonal antibodies are disclosed effective for the treatment of **HCV** infections together with methods for treating Hepatitis C virus infections or for the regulation of Hepatitis C virus production wherein said antibodies may be used.

L6 ANSWER 7 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:210744 BIOSIS
DOCUMENT NUMBER: PREV200600212473
TITLE: Retinoic acid causes up-regulation of the **gastrointestinal glutathione peroxidase** (GI-GPx) promoter and concomitantly down-regulation of hepatitis C virus (**HCV**) subgenomic RNA.
AUTHOR(S): Herget, T.; Morbitzer, M.; Klebl, B.; Galle, Peter; Becher, Wulf; Wallasch, Christian
SOURCE: Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A699.
Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 2006
Last Updated on STN: 29 Mar 2006

AB The mRNA expression patterns of three Hepatitis C Virus (**HCV**)-subgenomic RNA replicon cell lines were compared with those of mock transfected or untransfected HuH7 cells utilizing cDNA array filters. The **gastrointestinal-glutathione peroxidase** (GI-GPx) mRNA was drastically down-regulated (as low as 5 to 10% of controls) in all replicon cell lines, while the expression level of the classical cellular-**glutathione peroxidase** (cGPx) remained unaffected. These data were confirmed by Northern blot and Western blot analyses. GI-GPx is a selenoprotein belonging to a family of four members, responsible for the detoxification of peroxides.Measuring total cellular **glutathione peroxidase** activity, revealed that the replicon cells showed reduced **glutathione peroxidase** activity (approx. 50% of control cells). Accordingly, replicon cells demonstrated increased susceptibility towards paraquat, a compound producing oxidative stress, reflected by a reduced viability of the replicon cultures compared to mock-transfected cell lines.When replicon cells were incubated with interferon for four days to induce the innate immune response, the **HCV**-replicon became down-regulated. Concomitantly, expression of CI-GPx resumed to nearly normal levels. Interferon itself did not effect the expression of GI-GPx in mock transfected and naive HuH7 cells.Furthermore, transient over-expression of the GI-GPx cDNA via adenoviral gene transfer induced a substantial and consistent down-regulation of the **HCV** RNA and the NS5a protein in replicon cells. In depth inspection of the 5' promoter region of the

GI-GPx gene revealed the presence of two retinoic acid response elements (RARE). Treating replicon cultures with retinoic acid in the presence of selenite lead to increased expression of endogenous GI-GPx, followed by a dramatic down-regulation of the replicon. This decrease was even more pronounced, when cells were incubated with retinoic acid in the presence of selenite and interferon alpha.Taken together, these data show, that (a) expression of GI-GPx and replication of **HCV** exclude each other and (b) retinoic acid might be a valuable tool for the treatment Of **HCV** patients. Therefore, a clinical pilot trial at the University of Mainz with 9 population of interferon non-responders was initiated. Preliminary data of this clinical trial will be presented in parallel.

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ACCESSION NUMBER: 2006:210736 BIOSIS
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TITLE: All-trans-retinoic acid for treatment of patients with chronic hepatitis C and non-response to interferon alfa/ribavirin.
AUTHOR(S): Becher, Wulf O.; Wallasch, Christian; Herget, T.; Klebl, B. M.; Galle, Peter R.; Strand, D.
SOURCE: Gastroenterology, (APR 2005) Vol. 128, No. 4, Suppl. 2, pp. A697-A698.
Meeting Info.: Annual Meeting of the American-Gastroenterological-Association/Digestive-Disease-Week. Chicago, IL, USA. May 14 -19, 2005. Amer Gastroenterol Assoc.
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AB Introduction: In vitro studies, submitted in parallel by Herget et al, have shown that all-trans retinoic acid (ATRA) induces upregulation of selenium dependent **gastrointestinal-glutathione peroxidase** in **HCV**-subgenomic RNA replicon cells leading to drastic downregulation of the replicon, that was further enhanced by interferon alfa. Based on these findings, a clinical pilot trial was performed in **HCV** non-responder patients. Methods: 20 patients with chronic **HCV** infection and non-response to IFN alfa and ribavirin (pos. PCR at week 12) were randomly assigned to treatment with daily 45 mg/m2 ATRA p.o. and 30 mcg/d selenite (arm A) or 45 mg/m2 ATRA and selenite combined with 180 mcg/week peg-interferon alfa2a (arm B). All patients had serotype-1, elevated ALT levels and 9 patients had F3 fibrosis or cirrhosis. Mean IFNa pretreatment duration was 14 months, 9 patients were Peg-IFN nonresponders. ATRA treatment was continued for 12 weeks and followed for additional 12 weeks after end of treatment (ETR). **HCV** RNA was assessed by quantitative real time PCR.

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TITLE: Expression of **gastrointestinal glutathione peroxidase** is inversely correlated to the presence of hepatitis C virus subgenomic RNA in human liver cells.
AUTHOR(S): Morbitzer, Monika; Herget, Thomas [Reprint Author]
CORPORATE SOURCE: Merck KGaA, Frankfurter Str 250, D-64293 Darmstadt, Germany
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AB There is great medical need to develop novel therapies for treatment of human hepatitis C virus (**HCV**). By gene expression analysis of three **HCV**-subgenomic RNA replicon cell lines, we identified

cellular proteins whose expression is affected by the presence of **HCV** and therefore may serve as drug targets. Data from cDNA array filter hybridization, as well as from Northern and Western blotting, revealed that the **gastrointestinal-glutathione peroxidase** (GI-GPx) was drastically down-regulated (up to 20-fold) in all replicon cell lines tested. Concomitantly, total cellular **glutathione peroxidase** activity was drastically reduced, which rendered these human liver cells more susceptible toward oxidative stress. Interferon alpha caused down-regulation of the **HCV** -replicon followed by recovery of GI-GPx expression to nearly normal levels. Furthermore, expression of GI-GPx in replicon cells by gene transduction caused down-regulation of **HCV** RNA in a dose-dependent manner. Moreover, activating the endogenous gene coding for GI-GPx by all-trans-retinoic acid (RA) was sufficient to cause down-regulation of the **HCV** replicon. A small interfering RNA duplex abrogated GI-GPx up-regulation by RA and concomitantly suppression of **HCV**. The RA effect was dependent on the presence of sodium selenite, was reversible, and was independent of RNA-activated protein kinase. Taken together, these results show that **HCV** inhibits the expression of GI-GPx in replicon cells to promote its intracellular propagation. Modulation of GI-GPx activity may open new avenues of treatment for **HCV** patients.